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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,454	07/14/2004	Renir Eyjolfsson	2004-1082A	9421

513 7590 01/25/2008

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EXAMINER	
HOLT, ANDRIAE M	
ART UNIT	**PAPER NUMBER**
1616	

MAIL DATE	DELIVERY MODE
01/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,454	EYJOLFSSON, RENIR	
	Examiner	Art Unit	
	Andriae M. Holt	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner of record acknowledges receipt of the Applicant's Response, which was filed on October 19, 2007, in reply to the Official Action dated June 19, 2007.

Status of Claims

Claims 1-11 were pending in the application. Claim 11 has been amended. Claims 12-16 have been added.

Claims 1-16 will be examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 11 under 35 U.S.C. 112, related to the phase "including" being indefinite **is withdrawn** in view of Applicant's amendment of the claim by adding the phrase "consisting of".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-11 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Harris et al. (US 4,743,450) in view of Daniel et al. (WO 99/62560) **is maintained** for reasons of record and further articulated below.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al 4,743,450 in view of Daniel et al. WO99/62560.

The compound of formula 1 is the basic structure for an ACE Inhibitor, which is well known in the art, including the weight percentage ranges. Harris teaches the combination of formula 1, (col. 2, formula I, line 15-20), component b, an alkali or alkaline earth metal carbonate to be used as a stabilizer (col. 1, line 60 and col. 3, lines30-34), and saccharide compound used in the mixture (col. 1, line 61), the formulation by which the industry standard ace inhibitor, Accupril (Pfizer, Inc. and Warner Lambert, US Patent 4,743,450) is produced. Harris et al. does not specifically teach or make provision that the formulation does not contain a substantial amount of a saccharide compound. However, as defined in the specification of the instant application "a substantial amount of a saccharide compound" is any amount that would generally be considered to have a stabilizing effect on the active compound, such as more than about 10 wt % and more preferably including an amount which is more than about 5 wt% (page 3, lines 18-22). The wt % ranges for the provision of the instant invention are within the specification of Harris et al, 1% to about 90%, preferably about 10% to about 80% (col. 3, lines 56-58).

Harris et al. does not teach an insoluble alkaline-earth metal salt of hydrogen phosphate. Daniel et al., however, does teach a hydrolysis-minimizing agent suitable to retard hydrolysis in combination with an ACE inhibitor, which is susceptible to cyclization, hydrolysis, and/or discoloration, and (b) an effective amount of magnesium oxide suitable to retard cyclization, hydrolysis, and/or discoloration. Daniel et al. specifically sites as an example, dicalcium phosphate, a calcium mono hydrogen phosphate, that is insoluble in water (page 3, lines 20- 24).

It would have been obvious to one skilled in the art at the time of the

invention to have been motivated to combine the practices of the formulations of Harris et al. and Daniel et al. That is substituting the hydrolysis minimizing- agents, saccharides with an insoluble alkaline-earth metal salt of hydrogen phosphate. Each essentially performs the same function of retarding hydrolysis of an ACE inhibitor that is susceptible to hydrolysis. It has been discovered that useful, stable formulations can be produced using excipients comprising basic compounds as evidenced by the formulations produced by Harris et al. and Daniel et al. Each formulation using the basic compounds has been proven to be effective and efficacious ACE Inhibitors in reducing hypertension in patient populations. The use of these compounds in combination has proven to have greater storage stability and more suitable for use in drug combinations (Harris et al. col. 1 lines 36-38). The active ingredients or drugs contained therein are virtually preserved from cyclization and hydrolysis. In addition, the discoloration, which sometimes occurs when ACE inhibitors of this class are formulated and allowed to stand for significant periods of time, is minimized or eliminated completely (Harris et al col. 1, lines 27-33). It is well known in the art that it would be advantageous to manufacture stable ACE Inhibitor agents using basic compounds because these compounds are more cost effective to make or purchase.

In reference to claim 2, Harris et al, teaches the use of an alkaline stabilizer included in Group I and II of the periodic table combined with an anionic salt, magnesium, calcium and sodium are the preferred earth metals. Magnesium is most preferred. Carbonates are the preferred anionic salt (col. 3, lines 30-39). Harris et al. teaches claim 3 that the amount of alkaline earth metal carbonate is at least equal to the amount of the active compound of formula I, as evidenced by comparing example 1 of the instant invention (Specification, page 5, lines 5-15) and example 1 of Harris et al. (col. 4, lines 56-67). Claims 4 and 10 are taught by both references. Daniels et al., page 6, line 15, teaches enalapril and quinapril or, their corresponding free acids or pharmaceutically acceptable acid addition or base salts thereof. Harris et al., col. 2 lines 32-34, teaches enalapril and quinapril, their free acids or pharmaceutically acceptable acid addition or base salt thereof. These ace inhibitors are well known in the art. They each have very similar

properties, including the structure of Formula 1 in Harris et al. (col. 2, line 15, formula 1). The weight ranges in claim 5 are taught by Harris et al. (col. 2, lines 38-40). The total weight ranges for the total composition is 1% to about 70 %, preferably from about 1% to about 25 %.The weight ranges of claims 6 and 7 of the alkali or alkaline earth metal carbonate are taught by Harris et al. (col. 3, lines 40-44) as the quantity of stabilizer to be used will lie between about 1% and 90%, preferably about 10 % to about 80 %, encompassing ranges specified in the claims of the instant invention.

As per claims 8 and 9, Daniels et al., teaches the use of hydrolysis minimizing agents, including dicalcium phosphate, which is a calcium mono hydrogen phosphate, which is insoluble in water. The quantity of the hydrolysis- minimizing agent should be about 10% to about 95% preferably about 50% to about 95%, and most preferably 70% to about 90% (page 9, lines 5-17).

The suitable categories of drugs that can be combined in the embodiment of claim 11 of the instant invention are well known and well used in the art as categories that can be combined with ACE inhibitors, particularly quinapril, to provide an effective and efficacious anti-hypertensive agent with additive effects. Harris et al. and Daniel et al. teach claim 11 (Harris et al., col. 2, lines 60-68 and col. 3, lines 1-10; Daniel et al., page 7, lines 11-26).

Response to Arguments

Applicant's arguments filed October 19, 2007 have been fully considered but they are not persuasive. Applicant has traversed the instant rejection by stating that the cited references, Harris et al. and Daniel et al. combined do not solve the problem addressed by the instant invention that provides a formulation comprising a) the active ingredient, b) an alkali or alkaline earth metal carbonate, c) an insoluble alkaline-earth metal salt of hydrogen phosphate, and d) no substantial amount of a saccharide compound. Applicant submits that it would not have been obvious for the skilled person

to modify the teachings of Harris et al. in light of Daniel et al. Applicant further submits that in order to modify Harris et al. to arrive at the instant invention the skilled person has to (i) depart from using a substantial amount of saccharide, which is an essential feature of the Harris et al. invention, and (ii) use an insoluble alkaline-earth metal salt of hydrogen phosphate. The Examiner notes the discrepancy in the Office Action dated June 19, 2007, in the % weight ranges of the saccharide compound on page 3 of the action. The Examiner notes the correct % ranges as cited in Applicant's argument is from about 5% to about 90%, preferably about 10% to about 80% (Harris et al., col. 3, lines 57-59). The Examiner respectfully disagrees with Applicant's traversal argument in reference to the amount of saccharide in the composition. Harris et al. does teach a saccharide component to prevent hydrolysis and the examples cited show a significant amount of the saccharide component, as noted in Applicant's argument on page 6, however, in the specification Harris et al. teach the saccharide can be present in a range from about 5% to about 90%, which is within the range of "does not contain a substantial amount of a saccharide compound" of claim 1 of the instant invention, which is defined in Applicant's specification on page 3, lines 18-22, as " a substantial amount of a saccharide compound is any amount that would generally be considered to have a stabilizing effect on the active compound, such as more than about 10 wt % and more preferably including an amount which is more than about 5 wt%, or even more preferably including any amount of a saccharide compound which is more than about 2 wt%", which can be interpreted to mean an unsubstantial amount is an amount less than 10 wt %, more preferably less than 5 wt% or even more preferably including an

amount less than 2 wt%. Therefore, the % weight ranges of the saccharide compound, claimed in the instant application are taught by Harris et al., 5% to 90%.

In reference to Daniel et al., Daniel et al., though not in the examples, does teach that dicalcium phosphate, a calcium monohydrogen phosphate, can be used to retard hydrolysis in combination with an ACE inhibitor, which is susceptible to cyclization, hydrolysis, and/or discoloration (Daniel et al., page 3, lines 20-24). It would have been obvious to one skilled in the art to combine the teachings of Harris et al. and Daniel et al., as Harris et al. teaches it is within the skill in the art to have a formulation of an ACE inhibitor, an alkali or alkaline earth metal carbonate and saccharide to formulate a stable ACE inhibitor composition and Daniel et al. teaches it is within the skill in the art to use calcium monohydrogen phosphate as a substitution for the saccharide compound to retard cyclization, hydrolysis and discoloration.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-13 and 16 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Harris et al. (US 4,743,450) in view of Daniel et al. (WO 99/62560).

Applicant's Invention

Applicant claims a pharmaceutical formulation of compound a) an ACE inhibitor, b) an alkali or alkaline earth metal carbonate, c) an insoluble alkaline-earth metal salt of hydrogen phosphate, with the provisio that the formulation does not contain a substantial amount of a saccharide compound. Claims 13-16 define the amount of the saccharide compound as less than 10 wt%, less than 5 wt%, less than 2 wt% or does not contain a saccharide.

Determination of the scope of the content of the prior art (MPEP 2141.01)

The teachings of Harris et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed hereinabove. Harris et al. teach the quantity of the saccharide present will be from about 5% to about 90%, preferably about 10% to about 80% (col. 3, lines 56-58) (claim 13, less than 10 wt% of saccharide

compound, instant invention). Harris et al. further teach in example D, col. 5, lines 30-40 the preparation of a quinapril composition with no saccharide in the formulation (claim 16, formulation does not contain a saccharide compound, instant invention).

Differences between the prior art and the claims (MPEP 2141.02)

Harris et al. do not teach an insoluble alkaline-earth metal salt of hydrogen phosphate. It is for this reason Daniel et al. is joined.

The teachings of Daniel et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed hereinabove. The suitable categories of drugs that can be combined in the embodiment of claim 12 of the instant invention are well known and well used in the art as categories that can be combined with ACE inhibitors, particularly quinapril, to provide an effective and efficacious anti-hypertensive agent with additive effects. Harris et al. and Daniel et al. teach the specific drugs of claim 12, including hydrochlorothiazide, dextromethorphan, and dextromethorphan hydrobromide (Harris et al., col. 2, lines 60-68 and col. 3, lines 1-10; Daniel et al., page 7, lines 11-26).

Finding of Obviousness/Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the two cited references to produce a stable ACE inhibitor composition because Harris et al. teach it is within the skill of the art to make a stabilized ACE inhibitor composition comprising an ACE inhibitor, an alkali earth metal carbonate and a saccharide compound with a weight range between 5% and 90% and Daniel et al. teach that dicalcium phosphate can be used as a hydrolysis minimizing

agent, which performs the same function of retarding hydrolysis of an ACE inhibitor that is susceptible to hydrolysis. One would have been motivated to make the combination in order to receive the expected benefit of a useful, stable formulation of an ACE inhibitor that will be preserved from cyclization and hydrolysis. Given the state of the art as evidenced by the teachings of the cited references, and absent any evidence to the contrary, there would have been a reasonable expectation of success in combining the teachings of the cited references to produce an effective, efficacious and stable ACE inhibitor formulation.

Claims 14-15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art teaches away from a formulation of an ACE inhibitor composition that contains less than 5 wt% or less than 2 wt% of a saccharide compound.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andriae M. Holt whose telephone number is 571-272-9328. The examiner can normally be reached on 7:00 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richter Johann can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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